CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

BIFENOX

SB 950-126, Tolerance # 00351

August 4, 1988

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect.
Chronic toxicity, rat:	See: combined, rat
Chronic toxicity, dog:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, rat:	See: combined, rat
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome mutation:	No data gap, possible adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T880804
One-liners prepared by M. Silva, 8/4/88

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

Subchronic, Combined Rat

** 043 068217 "Bifenox: Preliminary Dose Range Finding Study in Rats by Dietary Administration For 4 Weeks," (Huntingdon Research Center, 11/2/84). Bifenox technical (purity not stated) was administered in diet for 4 weeks to Sprague-Dawley CD rats at 0, 1000, 2000, 3500, 5000 and 10,000 ppm (5/sex/group). NOEL = 2000 ppm (body weight gain was significantly decreased in males at 10,000 ppm; liver weights were significantly increased in females at $\geq$ 3500 ppm and in males at 10,000 ppm; livers appeared enlarged in males at $\geq$ 3500 ppm; centrilobular hepatocyte enlargement was observed in males at 10,000 ppm). **No adverse effect. Acceptable supplementary data for study 068216.** M. Silva, 6/30/88.

COMBINED, RAT

** 042 068216 "Bifenox: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats," (Huntingdon Research Center Ltd, 7/8/87). Bifenox technical (98% pure) was administered in diet to Sprague-Dawley rats at 0, 500, 1580, 5000 ppm (50/sex/group for oncogenicity; 20/sex/group for satellite) for 104 weeks. NOEL = 1580 (lower body weights and higher liver weights were observed in both sexes at 5000 ppm when compared to controls). No oncogenic effects were observed. **No adverse effect. Acceptable.** M. Silva, 7/5/88.

CHRONIC TOXICITY, RAT

See: COMBINED, RAT

CHRONIC TOXICITY, DOG

032 044511 "Bifenox: Oral Toxicity Study in Beagle Dogs (Repeated daily dosage for 52 weeks)," (Huntingdon Research Centre Ltd., 1/31/86). Bifenox technical (98% pure) was administered by capsule to Beagle dogs at 0 (vehicle = empty capsules), 20, 145 and 1000 mg/kg/day for 52 weeks (6/sex/group--of these animals, 2/sex/group were used for an interim kill at 26 weeks). **No adverse effect.** NOEL > 1000 mg/kg/day (no significant treatment-related effects were observed at any dose level). **Not acceptable** (an MTD was not reached). **Possibly upgradeable** (justification of dose selection is requested). M. Silva, 7/7/88.

ONCOGENICITY, RAT

See: COMBINED, RAT

ONCOGENICITY, MOUSE

**** 019/020 961519** "24-Month Carcinogenicity Study in Mice," (Litton Bionetics, 6/82). Bifenox technical (98.3% pure) was administered in the diet to B6C3F1 mice at 0, 50, 200, and 1000 ppm (60/sex/group) for 24 months. NOEL = 200 ppm (males showed increased liver weights and females showed increased kidney weights at 1000 ppm with no accompanying histopathology; focal hypertrophy of convoluted kidney tubules was observed in males in a dose related manner but was viewed as focal enzyme induction). **Adverse effects** (significant increase in hepatic adenomas and carcinomas in males at 1000 ppm). EPA Reported in Pesticide & Toxic Chemical

News (5/6/87) that there was a delay in reporting adverse effects observed in a mouse oncogenicity study done at Litton Bionetics with Bifenox. The adverse effect data were not reported to EPA until 3 years after the study was completed. **Acceptable**. J. Remsen (Gee), 6/5/85. M. Silva, 7/8/88.

REPRODUCTION, RAT

038 046945 "Three-Generation Reproduction Study With Bifenox in Albino Rats," (Industrial Bio-Test Laboratories, Inc., 12/9/77). Bifenox technical (97.2) was administered in diet to CD rats at 0, 20, 60 and 200 ppm (10 males and 20 females/group) in a 3-generation reproduction study. **No adverse effect indicated**. Parental NOEL = 60 ppm (decreased liver weights in F2 females; relative liver weights were significantly decreased in both sexes of F2; F1 and F2 males showed increased gonad weights; F1 males showed increased spleen weights and relative spleen weights at 200 ppm). Reproductive NOEL = 60 ppm (decreased pup survival in F1b, F2a, F2b -21 days- and F3a-12 and 21 days; F3b showed lower number of pups-day 21; overall survival was down for F3a & b at all dose levels including the control; F3b showed a decreased live birth index). **Not acceptable** (no analysis of dosing material; in most cases, fewer than 20 litters/group were produced; randomization of animals was not described; weights of newborn pups should have been presented; necropsies should have been performed on all pups and adults). **Upgradeable** (CDFA requests an analysis of dosing material; a description of animal randomization process used; newborn pup weights). M. Silva, 7/12/88.

TERATOLOGY, RAT

** 041 068215 "Effect of Bifenox on Pregnancy of the Rat," (Huntingdon Research Centre Ltd., 6/23/87). Bifenox technical (purity = 98%) was administered by gavage to mated Crl:COBS CD(SD)BR rats at 0 (vehicle = 1% aqueous methylcellulose), 225, 900 and 3600 mg/kg/day (25/group) from day 6-15 of gestation (presence of sperm or vaginal plug = day 0 of gestation). **No adverse effect.** Maternal NOEL = 900 mg/kg/day (increased deaths; decreased food consumption; salivation, staining of mouth and patchy hair loss). Developmental NOEL = 3600 mg/kg/day (no significant effects observed at any dose). **Acceptable.** M. Silva, 7/13/88.

001 961521 "Teratogenic Study With MC-4379 (Methyl-5-(2', 4'-dichlorophenoxy)-2-nitrobenzoate) in Albino Rats," (Industrial Bio-Test Laboratories, Inc., 12/13/72). Bifenox technical (99% pure) was administered by gavage to mated Charles River rats (17-18/group) at 0 (vehicle = corn oil), 50 and 100 mg/kg during days 6-15 of gestation (day 0 of gestation = day of insemination). **No adverse effect indicated.** Maternal NOEL > 100 mg/kg (no effects were observed at any dose). Developmental NOEL > 100 mg/kg (no effects were observed at any dose). **Not acceptable** (no evidence of an MTD; no analysis of dosing solution; ratio of male to female fetuses and most individual data were not included in the report; no food consumption data, uterine weights, or macroscopic examinations on dams were presented). **Not upgradeable** (an MTD was not reached in this study). J. Remsen (Gee), 5/31/85.

014 961525 "Effect of Bifenox on the Pregnant Rat and Offspring During the Gestation and Lactation Periods (Report MOB 2/81562)," (Huntingdon Research Centre, 7/31/81). Bifenox technical (report stated: purity assumed to be 100%) was administered by gavage to mated CrL: COBS CD(SD)BR rats at 0 (vehicle = 1% methylcellulose) and 100 mg/kg/day (12/group) from day 6 of gestation to day 21 post partum (presence of a vaginal plug = day 0 of pregnancy). **No adverse effect indicated.** Maternal NOEL $\geq$ 100 mg/kg/day (a slight but non-significant decrease in relative and absolute liver weight was observed). Developmental NOEL > 100 mg/kg/day (no effects observed at 100 mg/kg/day). **Unacceptable** (an MTD was not reached in this study). **Insufficient information was provided to assess possible adverse effects. Not upgradeable.** Refer also to HRC report # MOB 1/81561 (record #961526) which provided

additional information relating to this study. J. Remsen (Gee), 6/4/85.

014 961526 "Effect of Bifenox on the Pregnant Rat and Offspring During the Gestation and Lactation Periods (Report MOB 1/81561)," (Huntingdon Research Centre, 7/31/81). Bifenox technical (report stated: purity assumed to be 100%) was administered in diet to mated CrL: COBS CD(SD)BR rats (24/group) at 0, 500 and 1000 ppm on day 6 to day 21 post-partum (presence of a vaginal plug = day 0 of gestation). Maternal NOEL > 1000 ppm (no significant effects were observed at any dose). Developmental NOEL > 1000 ppm (no effects were observed at any dose). **Unacceptable** (An MTD was not reached in this study). Insufficient information was provided to assess possible adverse effects. **Not upgradeable.** Refer also to HRC report # MOB 2/81562 (record #961525) which provides additional information relating to this study. J. Remsen (Gee), 6/4/85.

TERATOLOGY, RABBIT

** 029 044501 "Rabbit Teratology Study, Bifenox Technical, Revised Final Report," (Hazleton Laboratories America, Inc., 1/27/86). Bifenox technical (purity = 97%) was administered by gavage to artificially inseminated New Zealand White rabbits (16/group) at 0 (vehicle = 0.5% carboxymethylcellulose), 5, 50, 160, 500 and 1000 mg/kg/day on gestation days 6-19 (day of insemination = day 0 of gestation). **No adverse effects.** Maternal NOEL = 160 mg/kg/day (at 500 and 1000 mg/kg/day, hypoactivity, ashen or pale appearance, body tremors, and ataxia following initiation of treatment was observed; dose related mortality; transitory decreased body weight gain decrease was observed in the 500 and 1000 mg/kg/day group during treatment; food consumption was significantly decreased at 500 and 1000 mg/kg/day from day 6 of gestation). **Developmental NOEL =** > 500 mg/kg/day (no effects were observed at any dose. Due to excessive deaths in the 1000 mg/kg/day, fetal effects could not be evaluated in this treatment group). **Acceptable.** M. Silva, 7/13/88.

014 961522 "Teratology Study in Rabbits," (Hazleton Laboratories America, Inc., 2/12/79). Bifenox technical (98.3% pure) was administered by gavage to artificially inseminated New Zealand White rabbits at 0 (vehicle = corn oil), 100, 300 and 600 mg/kg/day from day 6-19 of gestation (day of insemination = day 0 of gestation). **Insufficient information to determine an adverse effect. Dosing was terminated on day 10 of gestation and the study was stopped shortly after that due to excessive mortality. Not acceptable** (the study was not completed). **Not upgradeable.** A subsequent dose range-finding study was then performed using 2 does/dose at 0, 12.5, 50, 100, 200, and 300 mg/kg to determine dose range for a subsequent teratology study. J. Remsen (Gee), 6/3/85.

** 014 961523 "Teratology Study in Rabbits," (Hazleton Laboratories America, Inc., 4/9/79). Bifenox technical (98.3% pure) was administered by gavage to artificially inseminated New Zealand White rabbits at 0 (vehicle = corn oil), 12.5, 25 and 50 mg/kg/day (15/group) during days 6-19 of gestation (day of insemination = day 0 of gestation). **No adverse effect.** Maternal NOEL $\leq$ 12.5 mg/kg/day (at $\geq$ 12.5 mg/kg/day an increase in mortality, depression, prostration, tremors, fecal and urine stains, nasal or eye discharge, soft feces, wheezing, cyanosis, ataxia, dyspnea, and hunched appearance was observed). Developmental NOEL > 50 mg/kg/day (no effects were observed at any dose). **Acceptable** (According to current standards of evaluation this study would not be acceptable due to a lack of analysis of dosing material). J. Remsen (Gee), 6/4/85.

GENE MUTATION

** 034 044521 "Salmonella/Microsome Mutagenesis Assay on Bifenox Technical," (American Biogenics Corporation, 2/26/86). Bifenox technical (purity = 99%) was used in a mutagenicity assay with and without enzyme activation at 0 (vehicle = DMSO), 0.06, 0.2, 0.6, 2, 6, 20 mg/plate

(no S-9) and 0.006, 0.02, 0.06, 0.2, 0.6, 1 mg/plate (+ S-9) using Salmonella bacterial strains TA98, TA100, TA1535, TA1537 and TA1538. The assay was then repeated using 0.1, 0.3, 0.5, 1, 3, and 5 mg/plate. In total, the assay was performed 3 times without activation (3rd assay with TA100, TA1537 & TA1538 only, using the same dose levels as in test 2) and 2 times with activation (triplicate plates/assay). **No adverse effect.** No increase in mutagenesis was observed with or without S-9 in any of the bacterial strains at any dose. Positive controls functioned as expected. **Acceptable.** M. Silva, 7/14/88.

** 027 038968 "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay," (Pharmakon Research International, Inc., 9/28/83). Bifenox technical was used on Chinese hamster ovary cells (duplicate cultures) at 30, 50, 100, 200 and 250 ug/ml (no S-9) or 50, 100, 300, 400 and 500 ug/ml (+S-9). **No adverse effect.** There were no mutagenic effects observed at any dose level, with or without activation. The positive controls functioned as expected. **Acceptable.** M. Silva, 7/15/88.

027 038969 "Mutagenic Activity in Salmonella typhimurium with Bifenox," (Borriston Laboratories, Inc., 12/23/83). Bifenox technical was used in a mutagenesis assay at 18, 54, 162, 486, and 1398 ug/plate with Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538. **No adverse effect indicated.** There was clearly no mutagenic effect at any dose for TA98, TA100, TA1537 and TA1538. **Unacceptable** (no purity of technical or analysis of dosing material; no individual data; positive control mutagenicity rates for benzo(a)pyrene--+S-9, N-methyl-N'-nitro-N-nitrosoguanidine--no S-9, and spontaneous reversion rates for tester strains were not those usually observed in this type of mutagenesis assay; no GLP or QA statements were included). **Possibly upgradeable** (submission of data for individual plate readings, QA or GLP statement, purity data on test material, analysis of dosing material and Borriston Laboratories historical spontaneous reversion rates and mutagenesis rates with positive controls for all the Salmonella strains used in this study are requested). M. Silva, 7/15/88.

013 961527 "Mutagenicity Testing on MC-4379 in Microbial Systems," (The Institute of Environmental Toxicology, Toxicology Division and Stanford Institute of Technology, 7/7/77). Bifenox technical (purity = 99.5%) was used in 2 tests: Test 1. Male ICR mice were treated by gavage in a host-mediated assay (2 equal doses over a 24 hour period at the rate of 0.2 ml/10 g) with 0 (vehicle = 5% Gum arabic), 300 and 1000 mg/kg. Immediately after the 2nd dose a 2 ml suspension of Salmonella typhimurium G46 (his^-) in logarithmic growth phase was injected IP. Animals were sacrificed 3 hours later. Test 2. Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, TA1538 both with and without activation were treated at 0 (vehicle = DMSO), 1, 10, 50, 100, 500, 1000 and 5000 ug/plate. **There was insufficient information in this study to assess possible adverse effects.** Test 1. No mutagenicity was observed at any dose level. **Not acceptable** (no individual data, no analysis of dosing solution, no rationale for dose selection and no toxicity observed to show bifenox reached the bacteria). Positive controls functioned as expected. Test 2. **Unacceptable** (no individual plate data; # of plates/treatment not indicated). Both studies are **possibly upgradeable** with submission of the missing data). J. Remsen (Gee), 6/3/85.

** 013 961530 "Bifenox - Mutagenicity Study Using Bacterial Strains," (Laboratory of Hokky Kagaku Kogyo, 3/82). Bifenox technical (purity = 99.5%) was used in a Salmonella typhimurium mutagenicity assay with and without activation at 0 (vehicle = DMSO), 10, 50, 100, 500, 1000, and 5000 ug/plate, using TA100, TA98, TA1535, TA1537 and TA1538. Bifenox was also tested with Escherichia coli strain WP2 uvrA at the same dose levels. **No adverse effect** (no mutagenic effects were observed at any dose). Positive controls reacted as expected. **Acceptable.** J. Remsen (Gee), 6/3/85.

013 961531 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenesis Assay Study #595-248-1," (EG & G Mason Research Institute, 5/4/79). Bifenox technical (purity not stated) was used in on tester strains TA100, TA98, TA1538, TA1535, TA1537 at 0 (vehicle =

DMSO), 100, 500, 2500, 5000 and 10,000 ug/plate (triplicate plates) both with and without activation. **No adverse effect indicated** (a precipitate formed at > 100 ug/plate and therefore the data at > 500 ug/plate is not usable, which leaves 1 concentration for mutagenicity evaluation; positive controls with and without S-9 were not run with all strains; according to Ames et al., expression of revertants/10^8 (reversion index) is not an appropriate measurement; no statistical analysis was performed; no QA or GLP statement). **Not upgradeable.** J. Remsen (Gee), 6/3/85.

013 961532 "Evaluation of Compound MCTR-12-79 (MRI #248) for Mutagenic Potential Employing the L5178Y TK+/- Mutagenesis Assay," (EG & G Mason Research Institute, 4/23/79). Bifenox technical (purity not stated) was used on L5178Y Mouse Lymphoma Cells at 0 (vehicle = acetone), 18, 24, 32, 42, 56, 75, 100 and 133 ug/ml (+ S-9) or 133, 178, 237, 316, 563, 750 and 1000 ug/ml (no S-9). **Insufficient information was provided in this report to assess a possible adverse effect.** No increased mutagenesis was observed at any dose. Positive controls functioned as expected. **Not acceptable** (inadequate protocol description; no statistical analysis; no purity information on the test article; no analysis of dosing material). **Upgradeable** (information lacking in the study should be provided). J. Remsen (Gee), 6/3/88.

CHROMOSOME MUTATION

**** 027 038971** "In vivo Micronucleus Assay in Mice with Bifenox," (Borriston Laboratories, Inc., 3/23/84). Bifenox technical (code no. 605) was administered to B6C3F1/BR mice in 2 intraperitoneal injections, 24 hours apart at 1440 mg/kg (80% the LD50), 960 and 480 mg/kg and animals were sacrificed at 48, 72 and 96 hours (4/sex/group/time point). All time points had positive and vehicle control groups. All females died by 48 hours in the 1440 mg/kg group, so the dosage administered was reduced to 720 mg/kg/injection (total of 1540 mg/kg in 2 injections) for females only. **Adverse effect** (an increased incidence in micronuclei was observed at 480 and 720 mg/kg/injection in females at 48 and 96 hours). No evidence of chromosomal damage was observed in males. **Acceptable.** M. Silva, 7/19/88.

** 027 038972 "In Vitro Chromosomal Aberration Assay on Bifenox Technical," (American Biogenics Corporation, 8/26/85). Bifenox technical (97% pure) was used on Chinese hamster ovary cells with and without activation for two exposure times: 8 hour exposure (no S-9) at 0 (vehicle = 1% DMSO), 25, 75, 250 and 750 ug/ml or 18 hour exposure (no S-9) at 0, 25, 75, 125, and 250 ug/ml. 2 hour exposure + 8 hour growth period (+S-9) at 0 (1% DMSO + S-9), 125, 250, 400, 1260 and 2510 or 2 hour exposure + 17 hour growth period (+S-9) at 0, 40, 75, 250, 400, and 750 ug/ml. **No adverse effect.** No significant increase in chromosome aberrations was observed at any dose with bifenox. The positive controls functioned as expected. **Acceptable.** M. Silva, 7/19/88.

013 961528 "Drosophila Mutagenicity Assays of Rhone-Poulenc Chemical Company Compound Bifenox (MRI #604)," (Microbiological Associates, 7/2/82). Drosophila was used to test the mutagenicity of bifenox technical (purity not stated) in a series of 4 assays. Test 1: Somatic Reversion of white-ivory where larvae are treated with test chemical for mutagenic activity, Test 2: Y Chromosome Loss where treated males are mated, Test 3: Dominant lethal mutations where eggs are treated with test chemical and eggs with unhatched larvae are scored, Test 4: Bithorax Test of Lewis where chromosome rearrangements are reflected in offspring phenotype. All test groups were treated with bifenox technical at 0.15 mg/ml in 5% ETOH. The # of flies/eggs/larvae scored, depended upon the test. (# scored = 1000 to 3500 flies) for mutagenic activity. **Possible adverse effect indicated** for chromosome rearrangements, since the Biothorax Test of Lewis was positive. None of the other tests showed positive effects. **Unacceptable** (no positive controls, no repeat of positive test, only one dose level was used, protocol was not in sufficient detail, data were in summary form only, no historical data, no rationale for number of flies/eggs/larvae scored. **Not upgradeable** (no positive controls to verify that the tests were working). J. Remsen (Gee), 6/3/85.

018 961533 "Metaphase Analysis of Rat Bone Marrow Cells Treated in vivo With Bifenox Technical," (Mobil Environmental and Health Science Laboratory, 6/24/81). Bifenox technical (98.3% pure) was administered in a single dose by gavage to Sprague-Dawley rats at 0 (vehicle = Methocel K4M Premium), 0.5, 1.0 and 1.5 gm/kg (6 males/group--5/group were used for metaphase analysis and 1 for absorption analysis). 5 bone marrow slides were made/animal and 50 cells were examined/animal for clastogenic effect. **No adverse effect indicated.** No increase in chromosomal effects was observed at any dose. **Not acceptable** (exact dosing schedule and sacrifice schedule unclear; unclear when bone marrow samples were taken; only one sex was tested; sampled at one time point only; 5 doses were given in 5 days--1 animal/group/day; no sign of toxicity from high dose so an MTD was not reached). **Not upgradeable** (MTD was not reached). J. Remsen (Gee), 6/3/88.

001 961534 "Mutagenic Study With MC-4379 in Albino Mice (Bifenox)," (Industrial Bio-Test Laboratories, Inc., 11/72). Not a guideline study. **Insufficient data to evaluate a possible adverse effect.** This is an invalid IBT study (#E2155). J. Remsen (Gee), 5/3/85.

Conclusion: Two (027 038971 and 013 961528) of the four studies showed adverse effects. Study 013 961528 showed one of four tests as being positive but had no positive controls to verify that tests were working and therefore the results are questionable. The study 027 038971 however was an in vivo assay which was acceptable and showed adverse effects. Study 018 961533 had no adverse effects but an MTD was not reached and there was no justification for dose selection. Study 001 961534 is an invalid IBT study and will not be considered in the evaluation of adverse effect and 027 038972 was an acceptable in vitro study which showed no adverse effects. Therefore, the two studies to consider would be 027 038971 and 027 038972. It is the decision of CDFA to consider 027 038971 in the evaluation of adverse effects since it is an in vivo study while 027 038972 was in vitro. Therefore bifenox should be considered positive for chromosome changes. M. Silva, 7/25/88.

DNA DAMAGE

027 038973 "DNA Damage in Bacillus subtilis with Bifenox," (Borriston Laboratories, Inc., 3/23/84). Bifenox technical (purity not given) was used in a spot test with cultures of B. subtilis tester strains at 0 (vehicle = DMSO), 18, 54, 162, 486, and 1398 ug/disc, incubated over night. Bacterial strains used were: rec^- strains recA1, recA8, recB2, recD3, recC5, recE4 and recG13, mc-1, and M45; Pol^- strains T-1 and TKJ8201; Exc^-, Rec^- and Pol^- strain HJ15; Exc-, Pol- and spore repair (Spp-) strain TKJ6321; and repair efficient strains HA101 and 168. A quantitative assessment of DNA damage by D37 was also run, using sensitive strains recB2, 168WT and TKJ8206. **No adverse effect indicated**. No effects were observed in the spot test or in the quantitative assessment test at any dose level. **Not acceptable** (no purity data on bifenox, dose level selection did not go high enough). **Not upgradeable.** M. Silva, 7/19/88.

** 013 961518 "An Evaluation of Carcinogenic Potential of MCTR-12-79 Employing the C3H/10T1/2 Cell Transformation System," (EG & G Mason Research Institute, 1/9/80). Bifenox technical was used on C3H/10T1/2 cells at 0 (vehicle = acetone), 4, 8, 16, and 32 ug/ml (12 plates/dose). A parallel toxicity test (4 plates/dose--same bifenox concentrations) was also run. Cells were treated for 18 hours, then toxicity plates were assayed for cloning efficiency after 10 days. The test plates were maintained on BME medium + 5% FBS for 35 days before being scored for transformation. **No adverse effect.** No cell transformation was observed at any dose. Positive control (DMBA) functioned as expected. **Acceptable.** J. Remsen (Gee), 6/3/85.

013 961535 "Evaluation of Bifenox Technical in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay," (Litton Bionetics, 5/81). Bifenox technical (lot #16230, MCTR-1-79; purity not stated) was used on rat hepatocytes at 0 (vehicle = DMSO), 0.5, 1.0, 2.5, 5, 10, 25, 50, 100 and 250 ug/ml (triplicate--50 cells/coverslip counted) for 18 hours. **No adverse effect indicated.**

No detectable UDS from 0.5 to 100 ug/ml (250 ug/ml was cytotoxic) was observed at 20-23 hours after initiation of treatment. The positive control functioned as expected. **Not acceptable** (no individual data, no statistical analysis, background was not subtracted, no historical data were presented). Upon receipt and evaluation of the requested information, the study is possibly **upgradeable.** J. Remsen (Gee), 6/3/85.

013 961527 "Mutagenicity Testing on MC-4379 in Microbial Systems," (The Institute of Environmental Toxicology, Toxicology Division and Stanford Institute of Technology, 7/7/77). Bifenox technical (purity = 99.5%) was placed on a filter paper disk and used at 0 (vehicle = DMSO), 20, 100, 200, 500, 1000 and 2000 ug/disk in a Rec-assay with recombination wild (H17) and deficient (M45) strains of Bacillus subtilis. Size of inhibition zone was measured after overnight incubation. **Insufficient information is provided in this study to assess possible adverse effects. Unacceptable** (# of replicates not indicated; no evidence of bifenox having reached the bacteria through the agar; no activation; no statistical analysis of data; no individual data; no QA statement included). **Not upgradeable** (no toxicity data or evidence bifenox reached the bacteria). J. Remsen (Gee), 6/3/85.

013 961536 "Mutagenicity Evaluation of Bifenox Technical LOT #16230, MCTR-1-79 in the Mitotic Recombination Assay with the Yeast Strain D5, Final Report," (Litton Bionetics, Inc., 8/81). Bifenox technical (purity not stated) was used on D5 strain of Saccaromyces cerevisiae with and without activation at 0 (vehicle = DMSO), 625, 1250, 2500, 5000 and 10,000 ug/tube (# of tubes/dose not indicated). **No adverse effect indicated. Not acceptable** (# of tubes/group not indicated; no statistical analysis; no individual data; DMSO is not recommended as a solvent in this assay). **Upgradeable** (above information must be provided for evaluation). J. Remsen (Gee), 6/3/85.

013 961537 "Bacterial DNA Damage/Repair Suspension Assay," (EG & G Mason Research, 10/2/79). Bifenox technical (purity not indicated) was used in a DNA repair assay on E. Coli strains WP2uvrA$^+$recA$^+$ and WP100uvrA$^-$recA and Salmonella typhimurium strains TA1978uvrB$^+$ and TA1538uvrB$^-$ at 0 (vehicle = DMSO), 417, 2083, 20834, and 41,667 ug/ml in liquid suspension (triplicate tubes) with and without activation. Subsequently, these same strains of bacteria were tested with bifenox at 0, 0.125, 1.25 12.5, and 125 mg/ml with and without activation. Survival was measured. **Insufficient information was provided for assessment of an adverse effect.** Survival in WP100 (uvrA$^-$recA$^-$) strain was decreased somewhat but due to solubility problems and lack of a clear dose response which was reproducible, interpretation is difficult. No effects on survival were observed with the other strains at any dose. **Not acceptable** (no purity of test material, data were not interpretable due to precipitation problems--solubility of compound was limited and therefore doses may not have been accurate; no statistical analysis of data). **Not upgradeable.** J. Remsen (Gee), 6/3/85.

NEUROTOXICITY

Not required at this time.

OTHER STUDIES

Metabolism

** 035 044522 "Biokinetics and Metabolism in the Male and Female Rat," (May & Baker Ltd., 4/86). Bifenox- C (radiochemical purity = 96%) and/or cold bifenox (purity = 99.8%) and administered to CD rats by stomach tube (vehicle = 0.25% aqueous gum tragacanth). Three tests were run. Test 1: A single dose of either 90 or 900 mg/kg ^{14}C-bifenox was administered to 5 rats/sex and urine and feces were collected every 24 hours for 7 subsequent days and recoveries

were done. Test 2: Once daily for 14 days, 90 mg/kg bifenox was administered to 5 rats/sex. On day 15, a single 90 mg/kg dose of ^{14}C-bifenox was given. Urine, feces and blood were monitored every 24 hours for 7 subsequent days and recoveries were done. Test 3: A single oral dose of ^{14}C-bifenox (90 mg/kg or 900 mg/kg) was administered to 5 rats/sex/group and the blood and plasma were monitored at 0.25, 0.5, 1.0, 2.0, 3.0, 5.0, 7.0, 21.5, 45.5, 69.5, 93.5, 118.0, 141.5, and 165.5 hours. **No adverse effect. Acceptable.** M. Silva, 7/14/88.

Acute Oral, Rat

** 033 044512 "Acute Oral Toxicity Study in Rats," (Bio/dynamics Inc., 10/2/85). Bifenox technical was administered to CD rats (5/sex) in an acute oral dose of 5000 mg/kg (vehicle = 1% methocel). **No observable abnormalities.** No deaths. LD50 > 5000 mg/kg (no effects were observed when compared to control, using the limit test). Toxicity Category IV. **Acceptable.** M. Silva, 7/20/88.

** 033 044516 "Acute Oral Toxicity Study in Rats," (Bio/dynamics, Inc., 9/23/85). Formulated bifenox (Modown 4F) was used in an acute oral toxicity study with CD rats, treated by intubation with a single 5000 mg/kg dose. **No observable abnormalities.** No deaths. LD50 > 5000 mg/kg (no effects observed with formulated material). Toxicity Category IV. **Acceptable.** M. Silva, 7/20/88.